THE COLLEGE OF RADIOGRAPHERS

Radiography (1998) **4**, 115–120

Prostatic cancer screening—does it fulfil the criteria for medical screening?

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Received 15 August 1997; accepted 25 January 1998

Keywords: Prostate cancer; population screening; prostate specific antigen (PSA); transrectal ultrasound (TRUS); digital rectal examination (DRE).

The criteria for a screening programme are used to critically review the extent to which a population screening for the early detection of prostatic cancer is feasible. Digital rectal examination (DRE), prostate specific antigen (PSA) measurements and transrectal ultrasound (TRUS) are three possible diagnostic procedures that are available. The sensitivity, specificity and positive predictive values of two of the tests, DRE and TRUS, are too low each to be considered on their own as a screening tool. A study completed in 1995 suggests that PSA on its own, with a sensitivity rate of 81%, is a highly discriminatory test for prostate cancer amongst healthy men, effectively predicting future cancers. However, until a randomized controlled clinical trial is undertaken to assess any possible reduction in morbidity and mortality rates from the disease, PSA measurement used as a screening tool is not yet justified. The conclusion points to the inappropriateness of a mass routine screening programme for this condition at the present state of knowledge.

Introduction

Prostate cancer is lately being seen as a major health problem in Western societies as it has been identified as the second most common cause of death from cancer after lung cancer [1]. At the time of writing there are no screening facilities for the early detection of prostatic cancer operating in the U.K., whilst some other European Union (EU) countries take a different approach; for example, population screening for this condition has been a policy in Germany since 1978 [2].

This article will critically review the extent to which a population screening programme for prostatic cancer would fulfil the criteria for a mass screening programme [3].

The criteria for screening [3]

The disease is common or can be identified as common in a particular subsection of the population

Prostate cancer is a growing health problem in most Western countries and world-wide there appears to be an increase in its appearance and the mortality arising from it [1]. Studies in the U.S.A. have suggested that the apparent rise in incidence of the disease is partially related to improvements in detection through the use of a commercially available test for prostate specific antigen (PSA) [4]. The use of this test therefore has resulted in more cancers being detected in middle-aged men as well as in elderly men. Two societies in the U.S.A., the American Cancer Society and the Urological Association have agreed to recommend that all men over the age of 50 years should be offered this test together with digital rectal examination (DRE) on an annual basis; in addition they recommend that younger men considered to be at high risk from the development of the disease should also be screened annually [5, 6]. The view of some researchers in the U.K. is that until any benefits are scientifically proven, through randomized controlled trials investigating mortality rates, quality of life and cost benefits, men should not be exposed to routine screening [7].

Where screening of younger men is favoured, the notion of high risk would include those with a

1078-8174/98/020115+06 $18.00/0

familial tendency towards the disease [8, 9]. Whilst genetic factors are thought to be important at younger ages i.e. <50 years, race also appears to be an important determinant of risk, with African American men at high risk and Asians at a lower risk [10]. There is, however, continued debate in the U.K. and Europe on the role played by environmental factors as a determinant of risk [11].

The disease is serious enough to warrant resources being spent

That it is a serious condition involving large numbers of men is not in dispute. Figures from the late 1980s and early 1990s indicate that there were 10 837 new cases of prostate cancer diagnosed in 1987 in England and Wales alone and in addition in 1993 there were 9530 recorded deaths in the U.K. from the disease [12]. Within the EU as a whole, it would appear that of all the cancers diagnosed in men, 13% were prostatic carcinomas, and 8.6% of all deaths due to cancer were attributable to this disease [2]. Although the condition predominates in elderly men, studies of mortality rates have revealed that an average of 9 years of life are lost through mortality from the disease [13].

On a cost utility basis, figures from a U.S.A. screening programme have estimated that the cost per crude and quality adjusted life year (QALY) gained from screening and treatment ranges from US$8400 to 23 000, with an estimated 1 to 2.68 QALY [14].

Early intervention arising from the screening programme results in: (a) a marked improvement in the quality of life or (b) increased life expectancy

At the present time in the EU, some 50–60% of all cases of prostate cancer present with metastatic disease or with locally confined disease which is too advanced to provide satisfactory curative measures [2]. Improvements in early detection through a range of tests and an awareness programme could ensure that more prostatic cancers are diagnosed before metastases set in, as is happening in the U.S.A. where the condition is the most frequently diagnosed male malignancy [1]. If a diagnosis is made of a locally confined palpable tumour prior to the onset of metastases and then treated by radiotherapy or prostatectomy, the 5-year survival rate has been shown to be 75–85%, with a life expectancy similar to an age-matched population free from the disease [15]. However, there appears to be little or no evidence to suggest that early diagnosis and treatment will lead to improvement of either disease-related mortality or to overall mortality in men [16]. Further, it has been observed that a one-off DRE and PSA measurement may only increase life expectancy in the age range 50 to 69 years by approximately 2 weeks, and in the over 69s by only a few days [17, 18]. Rather than the quality of life being improved, screening may result in some men being unnecessarily treated and the treatment itself leading to iatrogenic effects including impotence, incontinence or urethral stricture formation. Men need to be aware of the likelihood of some of these adverse effects in order to come to an informed decision on whether to undergo screening [19, 20].

The natural history of the disease should be understood so that the optimum stage for intervention can be identified

The anatomy of the gland and the disease processes affecting it are becoming more understood. Prostatic tumours arise most commonly in the peripheral zone of the gland (representing 70% volume) with benign prostatic hyperplasia (BPH) tending to develop in the transitional zone (5% volume) with the third zone, the central zone (25% volume), being fairly resistant to disease processes [6].

Prostate cancer in the early stages is progressive in all patients and the outcome of treatment to halt progression will depend on the stage at which it is identified. For localized prostatic cancer this will depend on the stage of the disease and the histological grade, which in turn will correspond to the volume of the disease [1]. It seems likely therefore, that the size of a primary tumour will determine local progression but not the ultimate survival rate of the individual. There is some evidence that the progression of the disease is more rapid in patients under 70 years than in older men [21]. Localized prostate cancer is thought to progress slowly, with an estimated doubling time of 2 years identified through PSA measurements [22]. A recent study of 49 261 healthy men involving the measurement of stored serum samples of PSA identified four out of five men who subsequently developed prostate

cancer. The conclusion was that 60–74-year-old men having a PSA concentration of 12 times the median had a 50% chance of developing the condition over the next 3 years [12].

The screening interval is such that it is shorter than the time taken for the fastest growing cancer to progress from being undetectable to being symptomatic

The clinical course of the disease is highly variable and a screening test should be able to show the presence of a cancer before symptoms appear [23]. Most latent carcinomas of the prostate which are found at post-mortem are focal, with a diameter of 1 to 2 cm and a volume of less than 0.05 ml and are thus not identifiable clinically [2]. It has been found, however, that concentrations of PSA may be raised for as long as 10 years before clinical manifestation of the condition [12].

Tumours identified through a combination of PSA and DRE or by trans-rectal ultrasound (TRUS) are usually 4 ml to 7 ml in volume. It has been suggested that all men over the age of 50 should have an annual DRE examination performed together with a PSA measurement, with the added recommendation that for men with a family history of the disease an annual PSA should first be introduced from the age of 40 [24]. An elevated PSA level (i.e. greater than 4 $ng.ml^{-1}$) is then seen as a positive indication for a TRUS examination [25].

The screening test should be accurate and reliable

It had been suggested until recently that the sensitivity, specificity and positive predictive values of each the diagnostic tests available (PSA, PSAD, DRE, TRUS) are too low to be considered each on their own as a screening test [2]. DRE, for example, has been shown to have accuracy, sensitivity and specificity rates of 79.9%, 91% and 73.8%, respectively. A combination measurement of PSA (>4 $ng.ml^{-1}$), DRE and TRUS has been shown to increase values for accuracy (84.2%) and sensitivity (91.2%) but not to increase specificity (71.4%) [26].

A fairly recent prospective observational study of stored serum samples of healthy men aged 60 years or more concluded that PSA measurements on their own could effectively predict future clinical prostate cancer [12]. A raised PSA is associated with benign prostatic hyperplasia (BPH) and it has been determined that for every gram of glandular BPH tissue, that PSA is raised by 0.3 $ng.ml^{-1}$ [22]. It would appear, however, that prostatic cancer elevates PSA 10 to 12 times as much as a similar volume of BPH [27]. PSA testing using total levels does have appreciable false-positive and false-negative results, particularly in the 2.5 to 10 $ng.ml^{-1}$ range. However, the selective measurement of percentage-free PSA has been shown to significantly improve the sensitivity of prostate cancer screening with PSA. A low percentage-free PSA (<10%) appears to be a powerful predictor of cancer even after two negative biopsies [28]. In addition, the percentage of free PSA may also correlate with the potential aggressiveness of early stage prostate cancer [29]. Free to total ratios may also be used to decrease biopsies in patients with intermediate PSA levels of 4 to 10 $ng.ml^{-1}$ [30, 31].

Clinicians have been advised that the act of digital rectal examination (DRE) and recent defaecation may elevate PSA values, although one study found that whilst the increase may be considered statistically significant it would not be of clinical significance [32]. The influence of ejaculation on serum levels of PSA appears not to affect concentrations in younger men [33], but causes a significant increase in levels of PSA in men 49 years to 79 years, increases that may persist for up to 48 h and which may thus have a bearing on the timing of PSA sample collection [34]. TRUS allows for accurate measurement of the prostate gland from which a PSAD value can be calculated (PSA divided by gland volume) which, if greater than 0.12, indicates a 10% probability of cancer being present [35]. It has been reported that in the majority of men over the age of 50 years an elevated PSA value subsequently investigated by TRUS reveals a benign condition [25]. Trans-rectal probes are able to produce high resolution images, which have the ability to locate quite small clinically impalpable nodules in the gland and once a nodule is detected a biopsy can be performed under ultrasound guidance, saving time and alleviating the anxiety of asking a patient to attend for a further visit [36].

The research undertaken by Parkes *et al.* [12] has shown that the ability to distinguish between healthy men who did and did not develop clinical

prostate cancer is possible through a single PSA measurement. Their study showed a false-positive rate of 0.5% for men under the age of 50 years, but that as age increases the false-positive rate rises and the detection rate falls. The odds that future cancers will develop amongst those men with raised levels of PSA will depend on, in addition to other factors, the prevalence rates in the particular age group. With a prevalence rate of prostate cancer in men aged 60–74 years of 0.8%, it was found that those with concentrations greater than or equal to 12 times the normal median had a 50% chance of developing cancer within 3 years.

Acceptable treatment and resources for treatment must be available

Treatment can take the form of radiotherapy, radical prostatectomy or hormonal treatment, although with some commentators claiming that no adequate study has yet been carried out to compare these alternatives [1]. Evaluation of the most appropriate treatment and the associated adverse effects, for example, incontinence, has yet to be undertaken [12].

One option to treatment is a 'wait and see' policy, especially in older men, as it is likely that amongst men in the older age group with localized prostatic cancer, death would be from causes other than cancer (60% other causes) [13]. So it is not yet certain that active treatment of a localized prostate cancer offers any advantages over surveillance [37]. The iatrogenic effects associated with treatment may be a deciding factor on whether treatment is considered or not.

From studies carried out on men at post-mortem, it has also been suggested that if all cancers discovered at post-mortem had been identified and treated prior to death that 26 out of 27 men would have been treated unnecessarily as the tumour would not have been life threatening [2]. Clearly, considerable resources would have to be made available to treat detected cancers as it could be considered ethically unsound not to treat detected lesions.

Discussion

Several developments have recently occurred which have resulted in a better understanding of the nature of prostate cancer and its detection. The developments are a serum assay for PSA and a greater understanding of the value of trans-rectal ultrasound. In addition, many men have become more aware of the prostate gland and the potential problems associated with it through the many reports in the media, which have highlighted the rise in the incidence of prostate cancer in Western societies. However, it has been suggested that the rise may be more apparent than actual, due to the fact that detection rates have improved greatly [1, 4]. Whether a routine screening service for the early detection of this condition is possible and or desirable has been the subject of much debate in both the EU and the U.S.A. There is, however, no consensus in Europe at the present time, with Germany, for example, having had a policy of screening for some 17 years and the U.K. yet to make any such recommendation. It is not yet known if the benefits, in terms of a reduction in mortality and morbidity rates, would justify the setting of a routine screening service [16]; and comparative rates between Germany and the U.K. are not forthcoming. In addition, it is thought that some locally confined lesions detected clinically will not be an immediate source of mortality as it has been calculated that the lifetime risk of detection of cancer will be 3.9%, with the risk of dying from the disease being 1.2%. This has led researchers to the conclusion that over-treatment could occur in two out of every three patients [2].

That prostate cancer is a serious disease is not in contention. It is the second most common cause of death from cancer in men, with a 1993 death toll in the U.K. of 9530 men, 90% of whom were over the age of 65 years [12]. For some time until the introduction of PSA radioimmunoassay kits for the measurement of PSA concentrations, detection of this condition was limited to a rectal examination (DRE), which had very low values of sensitivity and specificity. One study was able to identify that PSA concentration measurements improved detection rates of prostate cancer confined to the gland by as much as 78% over DRE alone [38]. A further subsequent prospective observational study in 1995 has shown that a distinction could be made between men who did and men who did not go on to develop prostate cancer from a single measurement of PSA in healthy men. It was concluded that men aged 60–74 years had a 50% chance of developing prostate cancer within 3 years of testing, if their PSA concentration was greater than or equal to 12 times the normal median. This led some

researchers to the conclusion that measurement of PSA concentration is sufficient as a screening test for healthy men over the age of 60 years to justify a randomized trial to determine whether treatment can lead to the reduction of morbidity and mortality rates [12].

Treatment of this condition can take many forms, including prostatectomy, radiotherapy or hormonal treatment, but there may also be a delayed 'wait and see' policy. However, having found the condition, the most appropriate treatment is not yet known, neither are the physical or psychological side effects arising from treatment, for example incontinence or impotence. Once the condition is detected, it would be ethically unsound not to provide treatment, especially to men in the younger age group; in addition, the provision of treatment to the older age group may also be ethically dubious in terms of any possible side effects, especially as the subsequent death of those older men with localized tumours is thought to be from causes other than cancer (60% other causes) [13]. Not all tumours are life-threatening; one study suggested that if all prostate cancers discovered at post-mortem had been identified and treated prior to death then 97% of men would have been treated unnecessarily [2]. Waterbor and Bueschen indicate that the problem with prostate cancer is that it is three diseases and not a single one and can take various forms (1) latent which will cause no harm, (2) progressive which will become symptomatic and can kill and (3) rapidly progressive, which is so highly malignant that it is likely to kill whether it is detected early or not [39]. The dilemma is whether to screen the whole population or a targeted group. The targeting of a specified age group to measure free and total PSA concentration levels would appear to be one appropriate way forward, so long as the deleterious effects of screen detection are weighed against the benefits. However, until the most appropriate treatment is known and until the possibility of any reduction in morbidity and mortality rates are known, a routine screening service is not justified especially in terms of the cost benefit ratio.

Conclusion

Tests are now available to assist in the detection of prostate cancer. PSA combined with DRE has been shown to improve detection rates by a considerable percentage over DRE alone [38]. However, it is also noted that an elevated PSA level is not a good discriminator for cancer as there are some factors that may elevate PSA including DRE itself, recent defaecation and inflammatory conditions of the gland and in younger men, post-ejaculation.

An elevated PSA value, especially if it is greater than 4.0 $ng.ml^{-1}$, is useful for providing an indicator for the third test, TRUS [25]. It is clear that each of these tests on their own could not be used as a screening tool; however, it is not known at the present time whether a combination of all three tests provides sufficient accuracy for a definitive diagnosis. Detection rates would improve if biopsies are performed under ultrasound control together with colour Doppler flow rate measurements. Whether such a battery of tests could or should be used as a screening programme is very much in doubt. The costs would be considerable, not just for detection, but also for the subsequent treatment of detected lesions. The most efficient prostate cancer screening method as yet remains undetermined. Until randomized clinical trials are carried out to estimate the advantages and reduced mortality rates arising from early detection and treatment, a wholesale population screening programme would appear to be inappropriate at this time.

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